REMARKS

Applicants thank Examiner Petersen and SPE Weber for the courtesies extended during a personal interview with the undersigned and inventors Darfler and Krizman on May 21, 2007. The claim amendments set forth above and the remarks below reflect the issues discussed during that interview.

Claims 1-39 are pending in the application. Claims 1, 5 and 6 have been amended. Claims 18-39 were previously withdrawn from consideration. The amendments to the claims are fully supported by the specification.

In the February 27, 2007 Office Action, claims 1, 5 and 6 were rejected under 35 U.S.C. § 112, second paragraph as indefinite. Claims 1-4 and 7-17 were rejected under 35 U.S.C. § 102 as anticipated by Banerjee et al. Claims 1-17 were rejected under 35 U.S.C. § 103(a) as obvious over Banerjee et al. in view of Ikeda et al. Claims 1-4 and 7-17 were rejected under 35 U.S.C. § 103(a) as obvious over Banerjee et al. in view of Kanai et al. Claims 1-4 and 7-17 were rejected under 35 U.S.C. § 103(a) as obvious over Banerjee et al. in view of Francis et al. The specific grounds for rejection, and Applicants' response thereto, are set forth in detail below.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement, Form PTO-1449, and the required fee are filed herewith.

Support for amendments

Support for the amendments to claim 1 is found at, *e.g.*, page 13, lines 11-12, and page 16, lines 23-25, of the specification. Support for the amendment to claims 5 and 6 is found in claim 1 as originally filed.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 1, 5, and 6 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. Specifically, the Examiner asserts that claim 1 recites "heating a composition… at a temperature and time sufficient to *negatively affect protein cross-linking* in said biological sample," and that the italicized phrase does not make clear if Applicants intended the reversal of crosslinking induced by formaldehyde, for example, or breaking of specific crosslinked bonds in protein

sample or another intended purpose. Office Action at page 3. Applicants have amended claim 1 herein to replace the term "negatively affect" with the term" reverse or release." Applicants assert that claim 1 as amended herein is definite, and request withdrawal of this rejection.

The Examiner indicated that claims 5 and 6 recite that the biological sample is heated to a specific temperature and time, but do not specify at what point in the method this step occurs, *i.e.*, it is unclear if claims 5 and 6 refer to step (a) of claim 1, or to any other time point in the method. Applicants have amended claims 5 and 6 herein to specify that the heating of the biological sample recited in these claims refers to step (a) of claim 1. Thus, Applicants assert that claims 5 and 6 as amended herein are definite, and request withdrawal of this rejection.

Rejections Under 35 U.S.C. §102

Claims 1-4 and 7-17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Banerjee et al ("Banerjee")(BioTechniques vol. 18:768-73, 1995). Applicants have amended claim 1 herein to specify that the biomolecule lysate is in soluble liquid form and suitable for protein expression analysis, and the content of the lysate is representative of the total protein content of the sample. Applicants traverse this rejection to the extent that it applies to claim 1 as amended herein and claims depending therefrom, for at least the following reasons.

The Examiner states that Banerjee teaches that "the samples can be extracted with phenol/chloroform/isoamyl alcohol, which can separate[] cell lysates into various fractions that a skilled artisan knows can be used for various biochemical assays, for example a DNA pellet and protein fraction." *Id.* Applicants respectfully disagree with the Examiner's characterization of the teachings of Banerjee. Banerjee is directed to methods for extraction of DNA, such as for PCR, that are not suitable for protein extraction. See, *e.g.*, Figure 1 of Banerjee. Specifically, Banerjee teaches the step of boiling the proteinase K-treated samples to denature residual protease and contaminating proteins. Banerjee at 772, emphasis added. This description makes clear that Banerjee does not teach preparation of a biomolecule lysate that is suitable for protein expression analysis. Instead, Banerjee teaches away from the present invention, describing two methods, boiling and phenol/chloroform/isoamyl alcohol extraction and precipitation, which the skilled artisan would recognize as being useful for DNA isolation but not for protein isolation and analysis.

The Examiner also states that Banerjee teach a method of retrieving useful analytes from paraffin-embedded tissue samples, including the step of microwaving the samples to melt and thereby separate the paraffin from the tissue. Office Action at page 4. The Examiner asserts that "[p]araffin melts at 56 degrees C, a temperature which can 'negatively affect' formaldehyde crosslinking of proteins." *Id.* Applicants respectfully disagree with the Examiner's contention that a temperature of 56°C is capable of negatively affecting (*e.g.*, reversing or releasing) formaldehyde crosslinks between proteins, and state that this contention is not supported by Banerjee or any other art of record. Accordingly, Banerjee does not teach the step of heating a composition comprising a histopathologically processed biological sample and a reaction buffer at a temperature and a time sufficient to reverse or release protein cross-linking in the biological sample, as required by instant claim 1.

For these reasons, Applicants assert that Banerjee fails to teach each and every step of amended claim 1 and accordingly, cannot anticipate claim 1. Claims 2-4 and 7-17 depend from claim 1, and contain all the limitations thereof. Since claim 1 is not anticipated by Banerjee, claims 2-4 and 7-17 also are not anticipated by this reference. Withdrawal of the rejection respectfully is requested.

Rejections Under 35 U.S.C. §103(a)

Banerjee *et al.* in view of Ikeda *et al.*

Claims 1-17 are rejected under 35 U.S.C. § 103(a) as obvious over Banerjee *et al.* in view of Ikeda *et al.* ("Ikeda")(J. Histochem. Cytochem. 46:397-403, 1998). Specifically, the Examiner states that while Banerjee does not expressly teach deparaffinizing samples with an organic solvent, heating a sample in a Triton X-100-containing incubation buffer, or heating a sample to 80-100°C for 10 minutes to 4 hours, Ikeda teaches these steps. The Examiner concludes that a person of skill in the art would have been motivated to extract various biomolecules from paraffin-embedded tissue using xylene deparaffinization followed by heat treatment in a Triton X-100-containing buffer because Banerjee teaches the generation of a multi-molecule lysate from formalin-fixed, paraffin-embedded tissue, and Ikeda teach that proteins can be extracted from such tissue by deparaffinizing in xylene, followed by heat treatment in a buffer containing Triton X-100. See Office Action at page 6. Applicants respectfully traverse.

The determination of obviousness under 35 U.S.C. § 103 requires an analysis of the four factual inquiries under *Graham*: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims at issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. *Graham v. John Deere*, 383 US 1, 17-18 (1966). Recently, the United States Supreme Court in the *KSR* decision recognized the continued usefulness of the "teaching, suggestion, or motivation" test in providing helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C.§ 103 (a). Moreover, the *KSR* court indicated the need for an explicit analysis of the "apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex, Inc.,* No. 04-1350 (U.S. April 30, 2007), slip op. at 14.

Banerjee does not teach or suggest methods of preparing a biomolecule lysate that is in a soluble liquid form suitable for protein expression analysis and where the content of the lysate is representative of the total protein content of the biological sample. Rather, Banerjee teaches away from preparing samples for protein assays, by characterizing proteins as contaminants. See Banerjee at 772. Moreover, Banerjee does not teach or suggest the step of heating the sample and a reaction buffer at a temperature and a time sufficient to reverse or release protein cross-linking in the biological sample, as required by amended claim 1. Instead, Banerjee teaches microwaving the samples at high power for 30-60 seconds, split into 15 second intervals. See Banerjee at 770. Finally, Banerjee does not teach or suggest the combination of heating a histopathologically processed biological sample in a reaction buffer at a temperature and a time sufficient to reverse or release protein cross-linking in said biological sample, and treating the heated sample with an effective amount of a proteolytic enzyme for a time sufficient to disrupt the tissue and cellular structure of said biological sample, so that the biomolecule lysate is suitable for protein expression analysis. For these reasons, Banerjee does not teach or suggest all the limitations of claim 1.

Ikeda does not cure these deficiencies. Ikeda teaches protein extraction from formalin-fixed, paraffin-embedded tissue samples by first deparaffinizing the samples in xylene then extracting the protein in a buffer containing Triton X-100, protease inhibitors (phenylmethylsulfonyl fluoride, aprotinin), either 0.1 or 2% SDS, at a temperature from 0°C to 100°C. See Ikeda at pages 398-99. Ikeda noted that protein could only be extracted when 2% SDS was used. *Id.* at 399. Ikeda does not teach or suggest treating the heated composition with

an effective amount of a proteolytic enzyme for a time sufficient to disrupt the tissue and cellular structure of said biological sample. Rather, Ikeda teaches away from protease treatment by the inclusion of multiple protease inhibitors. *Id.* Applicants assert that one of ordinary skill in the art would not have been motivated to combine the teachings of Banerjee and Ikeda. Moreover, even if the reference properly could be considered, the combination would not bring one to the steps of amended claim 1.

For these reasons, claim 1 as amended herein is not obvious in view of the combination of Banerjee and Ikeda. Claims 2-17 depend from claim 1, and contain all the limitations thereof. Since claim 1 is not obvious in view of Banerjee in combination with Ikeda, claims 2-17 are also not obvious in view of these references. Withdrawal of the rejection respectfully is requested.

Banerjee *et al.* in view of Kanai *et al.*

Claims 1-4 and 7-17 are rejected under 35 U.S.C. § 103(a) as obvious over Banerjee et al in view of Kanai et al ("Kanai")(Res. Vet. Sci. 64:57-61, 1998). Specifically, the Examiner states that while Banerjee does not expressly teach the use of trypsin to effectively treat formalin fixed tissue, Kanai teaches this step. See Office Action at pages 6-7. Applicants respectfully traverse.

The deficiencies of Banerjee are described above, and Kanai does nothing to remedy these deficiencies. Kanai teaches the treatment of deparaffinized sections with 0.025% trypsin for 30-120 minutes at 37°C. See Kanai at page 58. Kanai, like Banerjee, does not teach or suggest the step of heating a composition comprising a histopathologically processed biological sample and a reaction buffer at a temperature and a time sufficient to reverse or release protein cross-linking in the biological sample, as required by claim 1 as amended herein. Applicants assert that one of ordinary skill in the art would not have been motivated to combine the teachings of Banerjee and Kanai and that, even if one did, the combination of these references would not bring one to the steps of amended claim 1.

For these reasons, claim 1 as amended herein is not obvious in view of the combination of Banerjee and Kanai. Claims 2-4 and 7-17 depend from claim 1, and contain all the limitations thereof. Since claim 1 is not obvious in view of Banerjee in combination with Kanai, claims 2-4 and 7-17 are also not obvious in view of these references. Withdrawal of the rejection respectfully is requested.

Banerjee *et al.* in view of Francis *et al.*

Claims 1-4 and 7-17 are rejected under 35 U.S.C. § 103(a) as obvious over Banerjee *et al.* in view of Francis *et al.* ("Francis")(Biochem. J. 186:571-79, 1980). Specifically, the Examiner states that while Banerjee does not expressly teach the use of Triton X-100 in the proteinase digestion of a deparaffinized sample, Francis teaches that fresh (not formalin-fixed or paraffin-embedded) tissue samples can be treated with the combination of trypsin and Triton X-100 to solubilize and fractionate proteins. See Office Action at page 7. Applicants respectfully traverse.

The deficiencies of Banerjee are described above, and Francis fails to remedy these deficiencies. According to the Examiner, Francis teaches the treatment of microsomal particles with trypsin and Triton X-100 for 90 minutes at 37°C. See Francis at 572. Francis, like Banerjee, does not teach or suggest the step of heating a composition comprising a histopathologically processed biological sample and a reaction buffer at a temperature and a time sufficient to reverse or release protein cross-linking in the biological sample, as required by claim 1 as amended herein. Francis also does not teach or suggest that incubation of tissue of 90 minutes at 37°C results in the reversal or release of protein cross-linking; indeed, Francis does not disclose any protein cross-linking, as the tissue used was fresh. See Francis at 572. Applicants assert that one of ordinary skill in the art would not have been motivated to combine the teachings of Banerjee and Francis and that, even if the combination were proper, it would not have brought one to the steps of amended claim 1.

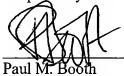
For at least these reasons, claim 1 as amended herein is not obvious in view of the combination of Banerjee and Francis. Claims 2-4 and 7-17 depend from claim 1, and contain all the limitations thereof. Since claim 1 is not obvious in view of Banerjee in combination with Francis, claims 2-4 and 7-17 are also not obvious in view of these references. Withdrawal of the rejection respectfully is requested.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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